Neurology-the next 10 years

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Abstract: Since the launch of our journal as Nature Clinical Practice Neurology in 2005, we have seen remarkable progress in many areas of neurology research, but what does the future hold? Will advances in basic research be translated into effective disease-modifying therapies, and will personalized medicine finally become a reality? For this special Viewpoint article, we invited a panel of Advisory Board members and other journal contributors to outline their research priorities and predictions in neurology for the next 10 years.

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FOCUS ON 10TH ANNIVERSARY

VIEWPOINT

Neurology—the next 10 years

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Abstract | Since the launch of our journal as *Nature Clinical Practice Neurology* in 2005, we have seen remarkable progress in many areas of neurology research, but what does the future hold? Will advances in basic research be translated into effective disease-modifying therapies, and will personalized medicine finally become a reality? For this special Viewpoint article, we invited a panel of Advisory Board members and other journal contributors to outline their research priorities and predictions in neurology for the next 10 years.

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Competing interests
R.B. declares associations with the following companies: Abbvie, Allergan, Astellas, Astra Zeneca, Bayer Schering, bioCSL, Biogen Idec, Boehringer Ingelheim, Bristol-Myers Squibb, Daiichi Sankyo, Desitin, Eisai, Eli Lilly, Esteve, Genzyme, Glenmark Pharmaceuticals, Grünenthal, Medtronic, Merck, MSD, Mundipharma, Novartis, Pfizer, Sanofi Aventis, Sanofi Pasteur, Teva, UCB. B.W. declares an association with Merck Serono. M.W. declares associations with the following companies: Acceleron, Actelion, Alpinia Institute, Bayer, Celldex, Immunocellular Therapeutics, Isarna, Magforce, MSD, Merck & Co, Northwest Biotherapeutics, Novocure, Pfizer, PIQUR, Roche, Teva. See the article online for full details of the relationships. D.F., G.B.F., C.B., Z.L.G., J.A.K., A.V., S.G.W. and S.J. declare no competing interests.

Pain

Ralf Baron

Research over the past decade has unravelled a variety of independently operating pain mechanisms, but our patients have not yet seen the fruits of this endeavour, and approval of new pain medications is rare. One reason for this state of affairs is the obvious heterogeneity of pain mechanisms. Thus, the potential of novel compounds addressing specific therapeutic targets is often obscured if a heterogeneous group of patients is included in trials that evaluate the average pain reduction for the entire cohort. The next decade will see dramatic changes in trial design, and in the clinical management of patients with pain.

When designing clinical trials, identification of the responding patient is an important factor. A complex cornucopia of clinical characteristics, including psychosocial factors, comorbidities, sensory abnormalities, and pathophysiological mechanisms, are likely to influence the overall response to pain treatment,[1,2] and the specific clinical response pattern depends on the drug or intervention used.[3] Statistical modelling of treatment response, using data from existing and new trials, should reveal certain clinical baseline profiles that will increase the likelihood of response. Knowledge about predictive pathophysiological mechanisms will, consequently, be translated back into basic research.

Relevant outcome parameters must also be determined. A commonly used end point in trials and in the clinic is the change in pain intensity averaged over the past 3 days. In reality, however, patients experience a complex temporal pattern of painful sensations. Some individuals perceive only a few severely painful attacks per day, in others the pain depends on movement, and often there are pain-free periods during the night. How can a patient calculate an average of these sensations over 3 days? Alternative outcome parameters that capture the individual pain-related quality of life and functionality need to be developed to account for the complex perception of pain and its consequences a precisely as possible.

For shared decision-making between patients and physicians, and in light of shrinking health resources, careful evaluation of the risks and benefits of pain management is a prerequisite. The above approaches will help us to successfully implement the individualization of pain therapy.

Child neurology

Donna Ferriero

We are witnessing an illuminating period in child neurology, and discoveries abound that will inform

practice and research for the next decade. The past 10 years saw the advent of therapeutic hypothermia for neonatal encephalopathy, and the results have been sufficiently enough to make this approach the standard of care in this scenario.[4] However, the protection afforded by therapeutic hypothermia is not complete, so the search for adjuvant therapies continues. The addition of erythropoietin to therapeutic hypothermia has shown promising results in early clinical trials, especially for perinatal stroke.[5] The use of stem cells represents another potential avenue to treat neonatal encephalopathy, and is being tested in pilot studies.[6] Cell-based therapies have also been used to correct inborn errors of metabolism, such as lysosomal storage diseases.[7]

Precision medicine will pave the way for more appropriate and targeted therapies in the next decade. *De novo* and rare inherited copy number variations (CNVs) are recognized to underlie the clinical manifestations of a growing list of neurodevelopmental conditions. For example, genome-wide analysis in cerebral palsy—not traditionally thought to be genetically determined—has uncovered a large number of chromosomal abnormalities associated with the disease.[8] These findings were substantiated in a recent study, which determined the impact of *de novo* CNVs on the diagnosis and classification of cerebral palsy.[9]

Similarly promising results have been obtained in other neurological conditions, including epileptic encephalopathies. The Epilepsy Phenome/Genome Project used exome-based sequence data to highlight novel candidate genes related to infantile spasms and Lennox–Gastaut syndrome.[10] Our understanding of the clinically heterogeneous neuromuscular disorders, such as the congenital muscular dystrophies, has also benefited from unbiased genomic approaches.[11]

A combined CNV and single-nucleotide variant data approach is expediting the discovery of new syndromes and genes involved in neuropsychiatric diseases associated with developmental delay, despite considerable genetic heterogeneity.[12] Perhaps the disease that has benefited most from novel technologies is autism: both *de novo* missense mutations and *de novo* likely gene-disrupting (LGD) mutations contribute to diagnosis.[13]

The next decade will be about leveraging the knowledge buried in genomics to define the causes of and treatments for paediatric neurological diseases.

Alzheimer disease

Giovanni B. Frisoni

If you wish to know where you are going, first ask yourself where you are coming from. A decade ago, patients with cognitive complaints typically consulted me after 3.5 years of cognitive symptoms, and diagnosis of Alzheimer disease (AD) was largely based on structural imaging (CT or MRI) to rule out secondary causes. Biomarkers such as cortical hypometabolism on 18F-FDG–PET, hippocampal atrophy on MRI, and cerebrospinal fluid (CSF) biomarkers (amyloid-β_{42} and tau) were reserved for the few with early symptoms or an unclear clinical picture. The typical patient diagnosed with AD had a mean Mini-Mental State Examination (MMSE) score of 20/30, treatment was based on symptomatic drugs only, and disappointment was still raging about the dramatic failure of AN1792, the first candidate AD modifier.[14]

My typical patient of 2015 has a history of cognitive complaints of 12 months or less. In my academic memory clinics, I use imaging and CSF biomarkers for most patients. In the context of real-life diagnostic research studies, I include quantitated and automated imaging biomarker readouts in the clinical reports (^{18}F-FDG–PET metrics of cortical hypometabolism, automated hippocampal volume extraction algorithms),[15] and I have access to molecular imaging biomarkers that allow *in vivo* neuropathological analysis (for example, amyloid PET).[16] Patients diagnosed with AD typically have an MMSE score of 25–26/30 and little or no disability, and all are given symptomatic drugs and are usually enrolled in clinical trials of second-generation anti-amyloid or anti-tau disease modifiers, some of which are providing early indications of effectiveness.[17,18]

In 2025, I expect that early diagnosis of AD with molecular (imaging and CSF) biomarkers will be daily practice in all memory clinics worldwide, and patients will be prescribed a cocktail of drugs aimed at both improving symptoms and delaying disease progression. The main efforts, however, will be directed towards asymptomatic people with the molecular signature of AD (brain amyloidosis or tau).[19] These individuals will be screened in the population with blood and genetic biomarkers,[20–22] and will be treated with disease modifiers to prevent the onset of cognitive symptoms and disability. This well-known disease-prevention paradigm is analogous to the treatment of hypertension and hypercholesterolaemia to prevent cardiovascular and cerebrovascular events.

The toughest challenge will be to promote brain health by changing lifestyles in the population. An impressive amount of evidence indicates that physical activity has multiple benefits for vascular, cognitive and emotional health;[23,24] however, people are reluctant to take up running, swimming or cycling for the sake of health alone. Scientists should stop advocating the need for yet another clinical trial on the cognitive benefits of healhy lifestyles,[23] and lobby decision-makers to implement societal policies to actively promote these lifestyles. This approach will substantially benefit not only the brain, but also society overall.

Neuro-oncology

Chetan Bettegowda & Ziya L. Gokaslan

The past decade has seen an explosion in the understanding of the molecular and genetic basis of dozens of tumour types, ignited by advances in our ability to study systems at a global level, and at an unprecedented pace. For many tumour types, our improved knowledge of the tumour–host interaction, the critical pathways that lead to tumorigenesis, and the mechanisms that underlie treatment response and resistance have led to the development of new therapies, including those that modulate the immune system or target specific genetic alterations. These discoveries have led to dramatic improvements in outcomes for a number of cancer types. Unfortunately, although the scientific advances in neuro-oncology have kept pace with those in other areas of oncology, the translation of this knowledge has been slow to improve patient outcomes.

Median survival for glioblastoma, the most common brain cancer, remains measured in months, with nearly all patients eventually succumbing to the disease. There is a dearth of FDA-approved therapies for nearly all CNS malignancies. One factor in our inability to adequately treat these tumours is the failure of historical classification methods to appreciate their complexity. Within any broad category of cancers affecting the CNS, genetic, epigenetic and proteomic profiling has revealed the existence of multiple subtypes.[25] These molecular characteristics can be predictive and prognostic, and have already begun to guide treatment selection in certain patient populations, such as SMO inhibitors in SHH-driven medulloblastoma, and tyrosine kinase inhibition in *BRAF*-mutant gliomas.[26,27]

In the next 10 years, we anticipate that the pathological diagnosis of CNS tumours will incorporate routine comprehensive molecular characterization. The knowledge derived from such detailed investigations of tumour specimens will enable significant advances, providing the basis for novel therapeutic and diagnostic strategies. CNS malignancies fall into the category of rare diseases, with each affecting only a few thousand individuals around the world, making appropriate clinical trials difficult to conduct. Grouping of patients into well-curated populations that are comparable at the subcellular level will allow the execution of clinical trials in populations that are most likely to benefit. These advances will, hopefully, lead to the improvements in survival that we are all so desperate to witness.

Regenerative neurology

John A. Kessler

The field of neurological therapeutics has blossomed over the past decade, with therapies that can both prevent disease progression and treat symptoms, but at present no techniques are available for regenerating the damaged nervous system. The next decade will witness the advent of regenerative neurology, a broad term that encompasses regeneration, replacement and/or engineering of cells to restore normal nervous system function. This change will reflect the convergence of advances in stem cell biology, gene therapy, materials science and nanotechnology, and gene-editing techniques (for example, the TALENS and CRISPR–Cas9 gene-editing platforms).[28,29]

Clinical trials of different types of stem cells have already commenced for neurological disorders including spinal cord injury, stroke, amyotrophic lateral sclerosis, multiple sclerosis, several genetic enzyme deficiencies, and other diseases.[30,31] Similarly, numerous gene therapy trials have been conducted for a spectrum of disorders, including Parkinson disease, brain tumours, diabetic neuropathy, genetic enzyme deficiencies, and Alzheimer disease.[32–34]

Although these early trials might demonstrate some clinical benefits, their efficacy will be limited by both technical and biological constraints, and strategies that combine new technologies are likely to be required. For example, stem cells require a highly regulated microenvironment, or ‘niche’, to survive, differentiate and integrate—an issue that is not addressed by current trials. Biomaterials can be designed to promote transplant survival and integration, both by providing the necessary cell–matrix interactions and through localized delivery of drugs or proteins.[35,36] Convergent technologies will be

required to explore the potential of RNA interference or short hairpin RNAs to knock down levels of mutant proteins in inherited neurological diseases[37] or, even more remarkably, to correct the defective gene sequences via gene-editing techniques.[28,29] This effort will require new vectors—both viral and nonviral—that are being developed to overcome the problems that have impeded gene therapy to date.[32,33] The advent of such combinatorial approaches in the next decade will help to launch a new era of regenerative neurology.

Epilepsy

Annamaria Vezzani

Epilepsy is a devastating neurological disease that afflicts approximately 1% of the world's population. Over the past 10 years, working as a basic scientist in the field of experimental epilepsy, I have witnessed the emergence of important new knowledge related to the basic mechanisms of the generation and recurrence of epileptic seizures—the main hallmark of epilepsy. Studies in animal models and *in vitro* brain cell and slice preparations have been instrumental in deepening our understanding of the molecules and pathways involved in the pathogenesis of seizures, and in the adaptive changes that the brain undergoes to re-establish homeostasis and promote repair.[38,39] These mechanisms represent an invaluable source of potential targets for drug and biomarker discovery.

Unfortunately, the development of new therapies lags behind the advances in basic research. In around 40% of people with epilepsy, the seizures cannot be controlled by the available antiepileptic drugs (AEDs). Even in responsive patients, the AEDs mainly provide symptomatic control of seizures, and often produce serious adverse effects.[40,41] Next-generation therapies need to have disease-modifying properties to halt or reverse the progression of epilepsy, or to prevent its onset in susceptible individuals. This unmet clinical need represents a translational research priority for the next decade. In addition, an intensive search is underway for EEG, imaging and circulating biomarkers of epilepsy onset and prognosis, and for prediction of the therapeutic effects of drugs.[42,43] The availability of biomarkers will be instrumental in the development of a new generation of therapies that are better targeted to the brain pathological processes in people who have epilepsy or are at high risk of developing the disease.

In the coming years, substantial efforts will be devoted to addressing the pathogenic mechanisms underlying comorbidities such as cognitive deficits, depression and autism spectrum disorders, which severely affect quality of life in people with epilepsy, especially those in the paediatric population.[44] In the context of preclinical research, it will be critical to refine animal models of adult and paediatric epilepsies to improve biomarker validation and drug discovery.[45] In addition, novel approaches are being developed, including the use of simple model organisms such as zebrafish (*Danio rerio*) to model acute seizures and genetic epilepsies,[46] and the generation of patient-specific neurons through induced pluripotent stem cell reprogramming to facilitate the development of cell-based novel drugs.[47]

Finally, technological improvements in diagnostic and research tools are ongoing. These include more-sophisticated EEG recording modalities for monitoring and predicting seizures in patients, optogenetic-based approaches for halting seizures, new devices for delivering drugs on demand, and improved and novel noninvasive molecular brain imaging approaches.[40,48–51] This armamentarium, together with increasingly sensitive and informative 'omics' and genetic approaches,[52,53] will help us not only to increase our knowledge of this multifaceted and complex disease, but also to markedly improve the therapeutic options for patients.

Channelopathies

Stephen G. Waxman

The prototypical antiepileptic medication phenytoin was discovered nearly a century ago. When phenytoin was introduced into clinical practice, its mode of action was not understood, but we now know that it acts, in large part, by blocking sodium channels. Since the advent of phenytoin, a stream of additional compounds that target ion channels have been developed.

Over the past decade, the pace of progress has quickened. A remarkable convergence of genetics, ion channel biology and neurology has yielded dramatic and far-reaching advances in our understanding of ion channels and their roles in human disease. Ion channels are increasingly being implicated in epileptiform disorders, and sodium channels have been shown to have important pathogenetic roles in disorders including myotonias and periodic paralyses, migraine, and peripheral neuropathy.[54–58] Studies on channelopathies—disorders caused by mutations in genes encoding specific ion channels—have firmly established a role for sodium channels such as $Na_V1.7$ (encoded by

SCN9A) as central players in human pain.[59] In concert, therapeutic molecules that block specific subtypes of sodium channels while sparing others are under development.[60] Advanced techniques for atomic-level molecular modelling,[61] together with the solution of the crystal structure of prototypical bacterial sodium channels, have propelled molecular pharmacology to new levels.

The next decade promises to be even more exciting. In my opinion, we are likely to see rapid translation of these advances into the therapeutic realm. I predict that within the next 10 years, new, more-effective therapies for pain that target 'peripheral' molecules such as the sodium channels $Na_V1.7$, $Na_V1.8$ and $Na_V1.9$ will enter the clinical domain. Given that the target molecules are crucial for electrogenesis in peripheral pain-signalling neurons but have little, if any, role in the brain, these new pain medications should not affect the brain and, thus, will not have central adverse effects such as sedation, confusion, ataxia or diplopia, and will not have addictive potential. I also anticipate that new genomically guided approaches to chronic pain, in which medications are matched to the genomic make-up of the patient, will transform pain management from 'trial and error' to 'first time around'.

Finally, I believe that additional channelopathies of the nervous system are likely to soon be discovered soon. Evidence is emerging that $Na_V1.8$ sodium channels, which are not normally present within the cerebellum, are expressed by Purkinje neurons in patients with multiple sclerosis (MS).[62] This anomalous expression leads to mistuning of these critically important cerebellar output neurons, which in turn leads to clinical dysfunction. Experiments in animal models have already demonstrated that some of the symptoms produced by this channelopathy can be ameliorated by blocking the offending molecules.[63] Hopefully, these findings will provide a basis for development of new targeted therapies for MS.

Autoantibody-related disorders

Sven Jarius & Brigitte Wildemann

Over the past 10 years, we have witnessed the discovery of numerous autoantibody-related neurological disorders, and the field is still growing. Of particular importance was the identification of aquaporin-4 (AQP4), the most abundant water channel in the CNS, as an antibody target in patients with neuromyelitis optica spectrum disorders (NMOSD) and its *formes frustes*,[64] and the discovery of *N*-methyl-D-aspartate receptors (NMDARs) and the voltage-gated potassium channel (VGKC) complex proteins LGI1 and CASPR2 as antigens in limbic encephalitis.[65]

Testing for AQP4-IgG is of the utmost importance in the differential diagnosis of multiple sclerosis (MS), particularly if optic neuritis, myelitis (mostly longitudinally extensive) and/or brainstem encephalitis are present, as some treatments that have been shown to be beneficial in MS—for example, IFN-β, natalizumab and fingolimod—are considered to be ineffective or even detrimental in AQP4 encephalomyelitis. The availability of NMDAR-IgG and VGKC-complex-IgG testing has made it possible to identify patients with encephalitis who are likely to respond to immunotherapy.

In AQP4 and NMDAR encephalomyelitides, a direct pathogenic role of the respective antibodies is highly likely, and the therapeutic and prognostic implications have been formally demonstrated.[66,67] By contrast, the pathogenic impact of other antibodies with high differential diagnostic potential still needs to be studied in more detail. Further anti-neuronal reactivities identified over the past 10 years include, among others, antibodies to AMPAR, $GABA_BR$, $GABA_AR$, glycine receptors, mGluR5 and DPPX in encephalitis; ITPR1, Homer-3, CARP, PKCγ, and ARHGAP26 in cerebellitis (termed 'Medusa head ataxia'[68]); MUSK and LRP-4 in myasthenia gravis; and CASPR2 in neuromyotonia. Moreover, a new role in anti-AQP4-negative myelitis and optic neuritis was recently assigned to anti-myelin oligodendrocyte glycoprotein antibodies.[69]

These findings have substantially facilitated the laboratory diagnosis of neurological autoimmune disorders. However, the rapid increase in numbers of potentially useful antibody markers also presents considerable diagnostic challenges. Currently, a multitude of commercial and in-house assays are used, some of which might be insufficiently sensitive and/or specific.[70] Given the potentially dramatic therapeutic consequences of false test results, future research should focus not only on identifying new antibody markers, but also on developing highly standardized immunoassays. In this context, emphasis needs to be placed on implementation of regular (international) inter-laboratory comparison trials for the most important novel autoantibodies, as well on creating the necessary institutional structures to perform such trials in a manufacturer-independent fashion.

A particular threat lies in the discrepancy between the low prevalence of many of the newly described autoantibodies and the high number of tests requested in daily practice by physicians who

wish to offer their patients the most extensive diagnostic work-up available. However, testing for rare markers in large, unselected populations always carries the risk of an unfavourable ratio of false-positive to true-positive results, even if highly specific test methods are used. Therefore, the development of consensus guidelines on antibody testing in neurology, which inform physicians who are not experts in neuroimmunology about indications for antibody testing, seems warranted.

General neurology

Michael Weller

Over the past decade, neurology has evolved dramatically from a mainly diagnostic—and often considered largely academic—speciality into a broad-based clinical discipline with multiple ramifications and subspecializations, increasingly focused on innovative and targeted therapeutic interventions. The next decade will undoubtedly see even greater changes and challenges for a clinical discipline that combines highly specialized, complex interventions with patient care at the community level, across a wide range of countries with highly variable health-care systems and resources.

Some core areas of neurology have seen—and should continue to see—major therapeutic advances. Examples include deep brain stimulation and other interventional treatments in Parkinson disease,[71] highly effective (but also potentially dangerous) immune interventions in multiple sclerosis,[72] and the re-emergence of early multidisciplinary intervention, as well as an evolving area of neurorehabilitation, in stroke.[73,74] Other areas with a bright future include those where neurology is working closely with neighbouring disciplines, hopefully more often in a cooperative than a competing fashion. In dementia, for example, neurologists are collaborating with psychiatrists and geriatric specialists to determine how to distribute the workload of clinical research, intervention and care,[75] and how to prepare our ageing societies for this major socioeconomic challenge. Neuro-oncology is a prototypical multidisciplinary discipline, in which we anticipate major advances in technical (in particular, neurosurgical) and immunological interventions.[76]

Future challenges for the neurology field include a balanced focus on research, education and patient care, and the inevitable re-definition of the main duties of neurologists. We need to evaluate the importance of clinical examination skills, and technical expertise in neurology-associated techniques, such as ultrasound, EEG and electroneuromyography. In addition, we must weigh up the costs and benefits of the increasing repertoire of diagnostic resources.

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